

4. Regenerative Medicine

Stage	Technology Readiness Level	Definition
Ideation	TRL-1	Scientific findings are reviewed and assessed as a foundation for conceptualizing new technologies.
Proof of Principle	TRL-2	Development of Hypotheses and Experimental Protocol Designs - Hypothesis (es) generated, research plans and/or protocols are developed.
Proof of Concept demonstrated	TRL-3	<p>Target/Candidate Identification and their Characterization</p> <p>Mandatory registration of Institutional Committee for Stem Cell Research (ICSCR) and Institutional Ethics Committee (IEC), with National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT) and CDSCO respectively</p> <p>Begin research, data collection, and analysis in order to test hypothesis. Explore alternative concepts, identify and evaluate critical technologies and components.</p> <p>-Sample collection after informed consent from the voluntary donor and begin characterization of candidate(s).</p> <p>-Preliminary efficacy demonstrated <i>in vitro</i> and <i>in vivo</i>.</p> <ul style="list-style-type: none"> • Identify target and/or candidate. • Demonstrate <i>in vitro</i> activity of candidate(s) • Generate preliminary <i>in vivo</i> as proof-of-concept efficacy data (non-GLP).
Proof of concept established	TRL-4	<p>Candidate Optimization and Non-GLP <i>In Vivo</i> Demonstration of Activity and Efficacy</p> <p>Animal Models: Initiate development of appropriate and relevant animal model(s) for the desired indications and perform non-GLP <i>in vivo</i> toxicity and efficacy</p> <p>Assays: Initiate development of appropriate and relevant assays and associated reagents for the desired indications.</p> <p>Manufacturing: Manufacture laboratory-scale (i.e. non-GMP) quantities of bulk product and proposed formulated product.</p> <ul style="list-style-type: none"> • Demonstrate non-GLP <i>in vivo</i> activity and potential for efficacy consistent with the product's intended use (i.e. dose, schedule, duration, route of administration, and route).

		<ul style="list-style-type: none"> • Conduct initial non-GLP toxicity studies and determine pharmacodynamics and pharmacokinetics and/or immune response in appropriate animal models (as applicable). • Initiate experiments to determine assays, parameters, surrogate markers, correlates of protection, and endpoints to be used during non-clinical and clinical studies to further evaluate and characterize candidate(s).
Early stage validation	TRL-5	<p>Advanced Characterization of Candidate and Initiation of GMP Process Development</p> <p>Animal Models: Development of animal models for efficacy and dose-ranging studies.</p> <p>Assays: Initiate development of in-process assays and analytical methods for product characterization and release, including assessments of potency, purity, identity, strength, sterility, and quality as appropriate.</p> <p>Manufacturing: Initiate process development for small-scale manufacturing amenable to GMP.</p> <p>Target Product Profile: Draft preliminary Target Product Profile including shelf life, storage conditions, packaging and transport should be considered to ensure that anticipated use of the product is consistent with the intended use</p> <ul style="list-style-type: none"> • Demonstrate acceptable absorption, distribution, metabolism and Elimination characteristics and/or immune responses in non-GLP animal studies as necessary for IND filing (wherever required). • Continue establishing correlates of protection, endpoints, and/or surrogate markers for efficacy for use in future GLP studies in animal models. Identify minimally effective dose to facilitate determination of "humanized" dose <p>Application submitted to Cell Biology Based Therapeutic Drug Evaluation Committee (CBBTDEC) constituted by CDSCO for conduct of cell therapy based clinical trials.</p>
	TRL-6	<p>GMP Pilot Lot Production, IND Submission, and Phase 1 Clinical Trial(s)</p> <p>Animal Models: Continue animal model development via toxicology, pharmacology, and immunogenicity studies.</p> <p>Assays: Qualify assays for manufacturing quality control and immunogenicity, if applicable.</p> <p>Target Product Profile: Update Target Product Profile as appropriate.</p> <ul style="list-style-type: none"> • Conduct GLP non-clinical studies for toxicology, pharmacology, and immunogenicity as appropriate. <p>Manufacturing: Manufacture GMP-compliant pilot lots.</p>

		<p>Manufacture, release and conduct stability testing of GMP-compliant bulk and formulated product in support of the IND and clinical trial(s) and submit Investigational New Drug (IND) package to DCGI and conduct Phase 1 clinical trial(s) to determine the safety and pharmacokinetics of the clinical test article.</p> <ul style="list-style-type: none"> • Complete Phase 1 clinical trial(s) that establish an initial safety, pharmacokinetics and immunogenicity assessment as appropriate.
Late stage Validation	TRL-7	<p>Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)</p> <p>Scale-up and initiate validation of GMP manufacturing process. Conduct animal efficacy studies as appropriate for Conduct Phase 2 clinical trial(s).</p> <p>Animal Models: Refine animal model development in preparation for pivotal GLP animal efficacy studies.</p> <p>Assays: Validate assays for manufacturing quality control and immunogenicity if applicable.</p> <p>Manufacturing: Scale-up and validate GMP manufacturing process. Begin stability studies of the GMP product in a formulation, dosage form, and container consistent with Target Product Profile. Initiate manufacturing process validation and consistency lot production.</p> <p>Target Product Profile: Update Target Product Profile as appropriate.</p> <p>Conduct GLP animal efficacy studies as appropriate for the product at this stage.</p> <p>Complete expanded clinical safety trials as appropriate for the product (e.g., Phase 2)</p>

Pre-commercialization	TRL-8	<p>Completion of GMP Validation and Consistency Lot Manufacturing, Pivotal Animal Efficacy Studies or Clinical Trials³, and DCGI Approval or Licensure</p> <p>Finalize GMP manufacturing process. Complete pivotal animal efficacy studies or clinical trials (e.g., Phase 3), and/or expanded clinical safety trials as appropriate. Prepare and submit NDA/BLA.</p> <p>Manufacturing: Complete validation and manufacturing of consistency lots at a scale compatible with DCGI requirements. Complete stability studies in support of label expiry dating.</p> <p>Target Product Profile: Finalize Target Product Profile in preparation for FDA approval.</p> <p>Complete pivotal GLP animal efficacy studies or pivotal clinical trials (e.g., Phase 3), and any additional expanded clinical safety trials as appropriate for the product.</p> <p>Prepare and submit New Drug Application (NDA) or Biologics Licensing Application (BLA) to the DCGI.</p> <p>Obtain FDA approval or licensure</p>
Commercialization and post market studies	TRL-9	<p>Post-Licensure and Post-Approval Activities</p> <ul style="list-style-type: none"> Commence post-licensure/post-approval and Phase 4 studies (post-marketing commitments), such as safety surveillance, studies to support use in special populations, and clinical trials to confirm safety and efficacy as feasible and appropriate.